REMARKS

Claims 29-34 are pending in the subject application. No claim has been added, cancelled or amended herein.

In view of the arguments set forth below, applicant submits that the Examiner's rejections made in the October 27, 2003 Advisory Action have been overcome. Applicant therefore respectfully requests that the Examiner reconsider and withdraw these rejections.

The Claimed Invention

This invention provides a method for producing a monoclonal antibody from a tetroma cell formed by fusing a lymphoid cell capable of producing antibody with a trioma cell which does not produce any antibody, wherein the trioma cell is obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell. The use of a heteromyeloma cell to generate the fusion partner trioma cell was neither known nor suggested in the prior art.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 29-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Oestberg et al. (U.S. Patent No. 4,634,664) for the reasons elaborated upon in the "final" Office Action dated June 25, 2003.

The Examiner stated that Oestberg et al. teach use of a three cell-containing, xenogeneic hybridoma fusion partner that does not produce antibody, and the use of said cell as a fusion partner to produce monoclonal antibodies. While acknowledging that Oestberg et al. do not teach that their fusion partner cell is a "trioma"

as per the definition of the term in the specification (i.e., a cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell), the Examiner also stated that Oestberg et al. teach heteromyeloma cell fusion partners (e.g., mouse/human fused cells, citing claim 14) (emphasis added). The Examiner concluded that it would have been *prima facie* obvious, to one of ordinary skill in the art at the time the invention was made, to have produced the claimed method because Oestberg et al. teach the claimed method except for use of a trioma cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell.

In response, applicant respectfully traverses, and maintains that the Examiner has failed to establish a *prima facie* case of obviousness of claims 29-33. Pursuant to 35 U.S.C. §103(a):

> [a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

According to M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicant maintains that the Examiner has failed to satisfy all three prongs of the requirements for establishing a *prima facie*

case of obviousness. First, Oestberg et al., in combination with routine skill, does not provide any suggestion or motivation to make the subject invention using a heteromyeloma cell. Second, it does not provide any expectation of success in using a heteromyeloma cell. Third, this reference does not teach the claimed element of the use of a heteromyeloma cell in making the invention.

Applicant emphasizes that, contrary to the Examiner's statement (citing claim 14 in Oestberg et al.), Oestberg et al. does not teach a heteromyeloma cell fusion partner. As is evident from claim 14 quoted below, Oestberg et al. teaches a "xenogeneic hybridoma cell" (i.e., a heterohybridoma) which is not a heteromyeloma cell:

> 14. A method of producing the hybridoma cell line of claim 1 which comprises making a xenogeneic hybridoma cell drug resistant, and fusing this cell to an antibody producing cell which is genetically compatible with the non-transformed partner in the xenogeneic hybridoma and selecting a desired hybrid. (emphasis added)

Applicant notes that several additional passages in Oestberg et al.'s specification and claims as quoted below confirm that the xenogeneic hybridoma cell (i.e., heterohybridoma) of that invention is not a heteromyeloma:

> Hybridoma is the term applied to cells formed by fusion of an "immortalizing" cell (in particular a myeloma cell) to a "normal" non-transformed cell usually chosen for its ability to produce a particular substance (e.g. a lymphocyte cell to produce antibodies) to form a hybrid. Col. 1, lines 9-14. ... We have now found that by using a xenogeneic hybridoma cell as parent for further fusion to another cell it is possible to obtain a hybridoma of greatly improved stability. Col. 2, lines 44-47. ... In a particular aspect the xenogeneic hybridoma chosen as immortalizing cell is a myeloma hybrid which has lost its own ability to produce immunoglobulin. An example of such a xenogeneic hybridoma cell would be that between a myeloma

> cell and a lymphocyte cell. Col. 2, lines 58-62. ... The invention therefore also concerns a method of producing a stable hybridoma cell line which comprises making a xenogeneic hybridoma cell parent drug-resistant[,] fusing this to a substance producing cell which is genetically compatible with the non-myeloma partner in the xenogeneic hybridoma and selecting a desired hybrid. Col. 3, lines 44-50. ...
>
> I claim:
>
> 1. A hybridoma cell line comprising an immortalizing cell fused to a cell producing a predetermined human antibody, the immortalizing cell comprising a xenogeneic hybridoma cell fused from an immortalizing cell and a non-transformed partner cell, said human antibody producing cell being genetically compatible with said non-transformed partner cell.
> 2. A hybridoma cell line as claimed in claim 1 wherein the antibody producing cell is of the same species as the non-transformed partner in the xenogeneic hybridoma cell parent.
> 3. A hybridoma cell line as claimed in claim 2 wherein the antibody producing cell partner and the non-transformed partner in the xenogeneic hybridoma cell parent are of human origin. ...
> 13. A hybridoma cell line as claimed in claim 1 which comprises a xenogeneic hybridoma cell formed by fusion of a mouse myeloma cell with a human lymphocyte as parent cell and a pre-sensitized antibody producing human-lymphocyte as substance producing cell. (emphasis added)

These passages clearly indicate that Oestberg et al.'s heterohybridoma is generated from fusion of a myeloma from one species with a non-transformed cell (i.e., not a myeloma cell) from another species. Oestberg et al. neither teaches nor suggests the production of a heteromyeloma by fusion of a myeloma cell from one species with a myeloma cell from another species.

By contrast, applicant's trioma recited in claims 29 and 30 is made, in relevant part, by fusing a human myeloma cell with a mouse myeloma cell to form a heteromyeloma cell. It is this heteromyeloma cell, and not the heterohybridoma of Oestberg et

al., which is then fused with a human lymphoid cell to form a trioma fusion partner cell. This element of the claims, i.e., the use of a heteromyeloma cell, is not taught in Oestberg et al. The Examiner therefore fails to satisfy the third criterion, per M.P.E.P. §2142, for establishing a *prima facie* case of obviousness with respect to claims 29 and 30.

In the Advisory Action, the Examiner rejected applicant's contention that Oestberg et al. teach use of a heterohybridoma, not of a heteromyeloma, on the basis that the subject specification allegedly appears to define the terms, heterohybridoma and heteromyeloma, as interchangeable. The Examiner stated that the specification does not specifically define the terms heteromyeloma or heterohybridoma. The Examiner also stated that the specification, however, defines "trioma" as a cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell (citing page 23, lines 19-24 of the specification). The Examiner further stated that the specification also discloses that "[t]he present invention provides a trioma cell obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell" (citing page 3, lines 15-17). The Examiner asserted that the only way these two statements can be reconciled is if the two terms (i.e., human-murine hybridoma, a.k.a. heterohybridoma, and heteromyeloma) are used interchangeably.

Applicant disagrees with the Examiner's conclusion. As applicant has argued previously (see September 25, 2003 Communication In Response To June 25, 2003 Final Office Action), the Examiner's conclusion lacks merit for the following reasons.

First, as a factual matter, a heterohybridoma cell and a heteromyeloma cell are different types of cells, as is evident

from dictionary definitions of the terms. The descriptions of a heterohybridoma (see Oestberg et al., claim 13, reciting a xenogeneic hybridoma cell formed by fusion of a mouse myeloma cell with a human lymphocyte) versus a heteromyeloma (see subject specification, page 22, lines 8-14, and page 29, lines 3-14 and 30-32, describing heteromyeloma cells as hybrid cells formed by fusion of mouse myeloma and human myeloma cells) clearly indicate that different types of "trioma" cell lines are produced in Oestberg et al. and in the present application. Applicant notes that the Examiner has not identified any statement in the subject specification or in remarks made by applicant indicating that these two terms are synonymous or interchangeable.

Second, the two statements from the specification quoted by the Examiner are entirely consistent, and it is without merit to conclude that the terms heterohybridoma and heteromyeloma are used interchangeably in the specification. Specifically, the meanings of the terms as understood by one skilled in the art make clear that a heteromyeloma cell can be considered one type of heterohybridoma, but *only rarely* can a heterohybridoma be considered a heteromyeloma. Thus, it is incorrect to equate a general reference to a heterohybridoma (as in claim 14 of Oestberg et al.) with a specific reference to a heteromyeloma where the focus is on the specific properties and applications of a heteromyeloma cell. Indeed, page 3, lines 15-17 of the specification states that "[t]he present invention provides a trioma cell obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell."

In the Advisory Action, the Examiner stated that applicant had argued on page 5 of his September 29, 2003 Amendment that a heterohybridoma is not a heteromyeloma. The Examiner also stated that applicant had argued on page 6 of that Amendment that the

terms heterohybridoma and heteromyeloma encompass overlapping populations. The Examiner stated that the aforementioned statements are obviously not compatible.

Applicant respectfully disagrees with this interpretation of applicant's remarks by the Examiner and maintains, as explained below, that these two statements from the September 29, 2003 Amendment cited by the Examiner are entirely compatible and consistent. On page 5 of the Amendment, applicant relied on The *Dictionary of Cell and Molecular Biology* (Third edition, J.M. Lackie and J.A.T. Dow [1999] Academic Press, London; available online at http://www.mblab.gla.ac.uk/~julian/Dict.html) to show that a heterohybridoma is a cell hybrid in which a myeloma cell from one species is fused with a T- or B-lymphocyte from a different species, whereas a heteromyeloma is a neoplastic cell formed from the fusion of two neoplastic plasma cells from different species. Based on these definitions which reflect the ordinary meanings of the terms as known to one skilled in the art, applicant asserted that a heterohybridoma is therefore not a heteromyeloma, and that the terms are not, as the Examiner concluded from the specification, interchangeable. Applicant reiterates that the terms "heterohybridoma" and "heteromyeloma" do not describe *the same* cell populations.

In the interest of precision, applicant elaborated on page 6 of the September 29, 2003 Amendment on the relationship between a heterohybridoma and a heteromyeloma. Applicant explained that in the special case of generating a heterohybridoma where the B-lymphocyte fusion partner used is itself a neoplastic plasma cell (i.e., a myeloma cell), a heteromyeloma will be produced. Thus, in this special situation, it can be said that the two terms can encompass overlapping cell populations to the extent that heteromyeloma cells could be considered heterohybridomas.

However, as applicant has previously noted, heterohybridomas can only rarely be considered heteromyelomas. To summarize, a heterohybridoma and a heteromyeloma are distinct types of hybrid cells. Notwithstanding that a heteromyeloma may be considered to be a specific type of heterohybridoma, "heterohybridoma" and "heteromyeloma" are not equivalent terms. Applicant emphasizes, therefore, that it is incorrect to equate a general reference to a heterohybridoma (as in claim 14 of Oestberg et al.) with a reference to a heteromyeloma.

The Examiner cited M.P.E.P. §2173.05(a):

> TERMS USED CONTRARY TO THEIR ORDINARY MEANING MUST BE CLEARLY REDEFINED IN THE WRITTEN DESCRIPTION
>
> Consistent with the well-established axiom in patent law that a patentee or applicant is free to be his or her own lexicographer, a patentee or applicant may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms. See, e.g., *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) ("While we have held many times that a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," in such a situation the written description must clearly redefine a claim term "so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term."); *Hormone Research Foundation Inc. v. Genentech Inc.*, 904 F.2d 1558, 15 U.S.P.Q.2d 1039 (Fed. Cir. 1990). Accordingly, when there is more than one definition for a term, it is incumbent upon applicant to make clear which definition is being relied upon to claim the invention. Until the meaning of a term or phrase used in a claim is clear, a rejection under 35 U.S.C. 112, second paragraph is appropriate. It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art. *In re Barr*, 444 F.2d 588, 170 U.S.P.Q. 330 (C.C.P.A. 1971).

In response, applicant submits that this section of the M.P.E.P. supports his own arguments made above. Applicant has not

suggested the use of terms in a manner contrary to or inconsistent with one or more of their ordinary meanings. On the contrary, applicant maintains that the terms "heterohybridoma" and "heteromyeloma" should be given their ordinary meaning, as used in the subject specification and as defined, for example, in the aforementioned *Dictionary of Cell and Molecular Biology* (http://www.mblab.gla.ac.uk/~julian/Dict.html).

Applicant emphasizes that the specification consistently refers to the heteromyeloma cells provided in the subject invention as hybrid cells produced by the fusion of mouse myeloma and human myeloma cells (see, *inter alia*, page 29, lines 3-14 and 30-32; and page 22, lines 8-14). This meaning is consistent with the definition in The *Dictionary of Cell and Molecular Biology*. Further, the specification refers to a human-murine hybridoma (a.k.a. heterohybridoma) as an immortal cell line which results from the fusion of a murine myeloma or other murine tumor cell with a human lymphoid cell derived from a normal subject (see page 21, lines 31-35). This definition too is consistent with the dictionary definition and with the definition in Oestberg et al. (see Col. 1, lines 9-14; and Col. 2, lines 44-47 and 60-62). Applicant maintains that no statements in the passages cited by the Examiner or anywhere else in the specification are in conflict with those definitions.

The specification also repeatedly describes the origin of a trioma fusion partner cell from a heteromyeloma cell (see, *inter alia*, page 3, lines 15-17 and 30-34; page 9, lines 15-17; and page 10, lines 25-29). This heteromyeloma cell is different from and nonobvious over the heterohybridoma provided by Oestberg et al. (Oestberg et al., Col. 2, lines 60-62, and claims 1-3 and 13).

Indeed, the specification explicitly distinguishes between the

use of heterohybridomas, as described by Oestberg, and heteromyelomas as fusion partners. The specification states at page 2, lines 29-34:

> In order to improve growth characteristics and stability of humAb production, heterohybrids between mouse myeloma cells and human lymphocyte [i.e., heterohybridomas] (Oestberg L, and Pursch E., 1983) as well as heteromyelomas (Kozbor D, et. al., 1984) are used as the fusion partners. (emphasis added)

This statement confirms unequivocally that the terms "heterohybridoma" and "heteromyeloma," as used in the subject specification, refer to distinct groups of cells. Further, it clearly demonstrates that the terms are not used interchangeably in the specification as the Examiner alleges.

Pursuant to M.P.E.P. §2173.05(a), any deviation from the ordinary meaning of the terms "heteromyeloma" and "heterohybridoma," for example a suggestion that they may be used interchangeably, must be supported by a clear and deliberate statement to that effect in the specification. The subject specification contains no such statement precisely because no meaning, other than the ordinary meaning of the terms, is intended.

Applicant respectfully submits that the above remarks obviate the rejection of claims 29 and 30 under 35 U.S.C. §103(a), and requests that the Examiner reconsider and withdraw the rejections.

Claims 31-33 depend, directly or indirectly, from claim 29. Applicant therefore submits that the arguments made in relation to claims 29 and 30 also obviate the rejections of claims 31-33. Accordingly, applicant also requests that the Examiner reconsider and withdraw the rejection of claims 31-33 under 35 U.S.C. §103(a).

Conclusion

In view of the remarks made herein, applicant respectfully requests that the Examiner reconsider and withdraw the claim rejections set forth in the October 27, 2003 Advisory Action, and earnestly solicits allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $385.00 RCE filing fee, is deemed necessary in connection with the filing of this Communication and accompanying RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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